

## CLAIMS

What is claimed is:

1. A fusion protein comprising a structure represented by the following formula, from N-terminus to C-terminus, SAP-Fc1-L1-Fc2, wherein Fc1 is a first Fc domain sequence comprising hinge-CH2-CH3, L1 is a linker, and Fc2 is a second Fc domain sequence comprising hinge-CH2-CH3, wherein SAP is a human serum amyloid P (SAP) component protein, wherein Fc1 and Fc2 comprise an amino acid substitution at position C226 and/or C229 according to EU numbering.
2. The fusion protein of claim 1, wherein Fc1 and Fc2 comprise an amino acid substitution at position C226 and C229 according to EU numbering, optionally C226S and C229S.
3. The fusion protein of claim 1 or 2, wherein the fusion protein comprises the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 23, or SEQ ID NO: 24.
4. The fusion protein of claim 3, wherein the fusion protein comprises the amino acid sequence set forth in SEQ ID NO: 1 without the C-terminal lysine, SEQ ID NO: 2 without the C-terminal lysine, SEQ ID NO: 3 without the C-terminal lysine, SEQ ID NO: 4 without the C-terminal lysine, SEQ ID NO: 23 without the C-terminal lysine, or SEQ ID NO: 24 without the C-terminal lysine.
5. The fusion protein of claim 1 or 2, wherein the fusion protein comprises the polypeptide sequence of TNT146, TNT151, TNT155, TNT156, TNT170, or TNT171.
6. A fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide comprises a human serum amyloid P (SAP) component protein linked to the N-terminus of a first human Fc domain (Fc1), wherein the second polypeptide comprises a second human Fc domain (Fc2) but does not comprise a human SAP component protein, wherein the first and the second Fc domains form a dimer, and wherein ~~the~~ one of the two Fc domains comprises a knob mutation and the other Fc domain comprises a hole mutation.

7. The fusion protein of claim 6, wherein the first polypeptide comprises a knob mutation and the second polypeptide comprises a hole mutation.
8. The fusion protein of claim 7, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO: 8, or SEQ ID NO: 10 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:6 or SEQ ID NO:9.
9. The fusion protein of claim 8, wherein  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:5 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:6;  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:7 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:6;  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:8 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:9; or  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:10 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:9.
10. The fusion protein of claim 8, wherein  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:5 with or without the C-terminal lysine, and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:6 with or without the C-terminal lysine;  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:7 with or without the C-terminal lysine and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:6 with or without the C-terminal lysine;  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:8 with or without the C-terminal lysine and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:9 with or without the C-terminal lysine; or  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:10 with or without the C-terminal lysine and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:6, with or without the C-terminal lysine.

11. The fusion protein of claim 6, wherein the fusion protein comprises the first polypeptide and the second polypeptide sequences of TNT148, TNT152, TNT157, TNT158, TNT147, TNT159, TNT160, or TNT161 according to Table 2.
12. The fusion protein of claim 6, wherein the Fc domain of the first polypeptide comprises a hole mutation and the Fc domain of the second polypeptide comprises a knob mutation.
13. The fusion protein of claim 6, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID NO: 16 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 12 or SEQ ID NO: 15.
14. The fusion protein of claim 13, wherein  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:11 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:12;  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:13 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:12;  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:14 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:15;  
or  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:16 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:15.
15. The fusion protein of claim 13, wherein  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:11 with or without the C-terminal lysine and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:12 with or without the C-terminal lysine;  
the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:13 with or without the C-terminal lysine and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:12 with or without the C-terminal lysine;

the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:14 with or without the C-terminal lysine and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:15 with or without the C-terminal lysine; or

the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO:16 with or without the C-terminal lysine and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO:15 with or without the C-terminal lysine.

16. The fusion protein of claim 1 or claim 6, wherein the human SAP is a wild-type SAP, optionally comprising the amino acid sequence set forth in SEQ ID NO:17.

17. The fusion protein of claim 1 or claim 6, wherein the human SAP comprises an amino acid substitution at position N32 or N110 according to SEQ ID NO:17.

18. The fusion protein of claim 17, wherein the human SAP comprises the amino acid sequence set forth in SEQ ID NO: ~~19~~ 20.

19. The fusion protein of any one of claims 6, or 16-18 wherein Fc1 and Fc2 comprise an amino acid substitution at position C226 and/or C229 according to EU numbering.

20. The fusion protein of claim 19, wherein Fc1 and Fc2 comprise an amino acid substitution at position C226 and C229 according to EU numbering.

21. The fusion protein of any one of claims 1, 2, 6, or 16-20, wherein Fc1 and Fc2 comprise amino acid substitutions C226S and/or C229S, according to EU numbering.

22. The fusion protein of claim 21, wherein Fc1 and Fc2 comprise amino acid substitutions C226S and C229S, according to EU numbering.

23. The fusion protein of any one of claims 1, 2, 6, or 15-17, wherein Fc1 and/or Fc2 comprises an amino acid substitution at amino acid position 11 and/or 14, numbering according to the amino acid sequence of SEQ ID NO: 18.

24. The fusion protein of claim 23, wherein Fc1 and/or Fc2 comprises a serine residue at amino acid position 11 and/or 14, numbering according to the amino acid sequence of SEQ ID NO: 18.
25. The fusion protein of claim 23 or 24, wherein Fc1 and/or Fc2 comprises the amino acid sequence set forth in SEQ ID NO: 18.
26. The fusion protein of claim 1, 2, 6, or 16-18, wherein the first and/or second Fc domain comprises a mutation that reduces FcRn binding.
27. A fusion protein comprising a structure represented by the following formula, from N-terminus to C-terminus, Fc1-L1-Fc2, wherein Fc1 is a first Fc domain sequence comprising hinge-CH2-CH3, L1 is a linker, and Fc2 is a second Fc domain sequence comprising hinge-CH2-CH3, wherein Fc1 and Fc2 comprise amino acid substitutions C226S and/or C229S according to EU numbering, and/or wherein Fc1 and Fc2 comprise a serine residue at amino acid position 11 and/or 14, numbering according to the amino acid sequence of SEQ ID NO: 18.
28. The fusion protein of claim 27, wherein the fusion protein further comprises a human serum amyloid P (SAP) component protein at the N-terminus of the fusion protein.
29. The fusion protein of claim 28 wherein the human SAP is a wild-type SAP, optionally the amino acid sequence set forth in SEQ ID NO:17.
30. The fusion protein of claim 28, wherein the human SAP comprises an amino acid substitution at position N32 or N110 according to SEQ ID NO:17.
31. The fusion protein of claim 30, wherein the human SAP comprises the amino acid sequence set forth in SEQ ID NO: 20.
32. The fusion protein of any one of claims 1-31, wherein the fusion protein forms a pentamer or a deccamer.

33. The fusion protein of any one of claims 1-32, wherein the Fc1 and Fc2 are human Fc domains.
34. The fusion protein of any one of claims 1-33, wherein the Fc1 and Fc2 are human IgG1 Fc domains.
35. The fusion protein of any one of claims 1-34, wherein the fusion protein has reduced aggregation compared to a fusion protein lacking the one or more amino acid substitutions.
36. A pharmaceutical composition comprising the fusion protein of any one of claims 1-35, and a pharmaceutically acceptable carrier.
37. The pharmaceutical composition of claim 36, wherein at least 50% of the fusion protein is in a pentamer and/or a decamer.
38. Nucleic acid encoding the fusion protein of any one of claims 1-35.
39. A vector comprising the nucleic acid of claim 38.
40. A host cell comprising the nucleic acid of claim 38 or the vector of claim 39.
41. The host cell of claim 40, wherein the host cell is a CHO cell or a 293 cell.
42. A method of producing the fusion protein of any one of claims 1-35, comprising culturing a host cell comprising nucleic acid encoding the fusion protein under conditions to express the fusion protein.
43. The method of claim 42, wherein the host cell is a CHO cell or a 293 cell.
44. The method of claim 42 or claim 43, wherein the host cell does not glycosylate the SAP component protein.

45. Use of the fusion protein of any one of claims 1-35 in the manufacture of a medicament, wherein the medicament is for ~~A method of~~ treating an amyloid disease in an individual, ~~comprising administering the fusion protein of any one of claims 1-35 to the individual.~~
46. Use of a fusion protein produced by the method of any one of claims 42-44 in the manufacture of a medicament, wherein the medicament is for ~~A method of~~ treating an amyloid disease in an individual, ~~comprising administering a fusion protein produced by the method of any one of claims 42-44 to the individual~~
47. The method-use of claim 45 or claim 46, wherein the amyloid disease is selected from the group consisting of AA amyloidosis, AL amyloidosis, AH amyloidosis, A $\beta$  amyloidosis, ATTR amyloidosis, ALect2 amyloidosis, IAPP amyloidosis of type II diabetes, and Alzheimer's disease.
48. An SAP-Fc fusion protein produced by the method of any one of claims 42-~~45~~44.
49. The method-use of any one of claims 45-47, wherein the individual is a human.